UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,824	02/27/2001	David J Squirrell	1498-119	3738

7590 12/15/2004

Nixon & Vanderhye
8th Floor
1100 North Glebe Road
Arlington, VA 22201-4714

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,824	SQUIRRELL ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 28-30* is/are pending in the application.

4a) Of the above claim(s) *6,9-20 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8,21-25 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/27/01, 5/3/01, 10/16/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-26 and 28-30 are pending in the application.

[2] In order to clarify the record, it is noted that, while the claim groupings in the Office action mailed January 30, 2004 did not include canceled claim 27, the examiner incorrectly listed claim 27 as being pending in the Office action mailed January 30, 2004. However, applicants correctly note that claim 27 was canceled in the preliminary amendment filed February 27, 2001.

Lack of Unity

[3] Applicant's election with traverse of the invention of Group I(a), claims 1-5, 7-25, and 28-30, filed April 15, 2004, is acknowledged. The elected invention is drawn to the special technical feature of a protein variant of *Photinus pyralis* luciferase having increased thermostability, wherein the variation is at position 214 of *P. pyralis* luciferase, a nucleic acid encoding therefor, a vector, a cell, a plant, the first claimed method of use, *i.e.*, the use of a protein in a bioluminescent assay, and a kit.

RESPONSE TO ARGUMENT: Applicants argue the claimed luciferase polypeptides share a common structure. Applicants urge the examiner to appreciate that luciferases are highly conserved, are obtainable from a limited number of sources, and have a high degree of homology, citing Ye et al. (*Biochim Biophys Acta* 1339:39-52). Applicants argue there are many motifs within the amino acid sequences of luciferases that are commonly possessed, citing Figure 2 of Ye et al. Applicants allege

that the Office has previously recognized that luciferases from different sources share a common structure, citing US Patent 6,132,983. Applicants argue the claimed luciferases have a defined specific amino acid within these conserved sequences, which impacts thermostability and can be precisely identified by its common position in the protein structures. Applicants' argument is not found persuasive.

As stated in a previous Office action:

> According to PCT Rule 13.2 and to the guidelines in Section (f)(i)(B)(1) of Annex B of the PCT Administrative Instructions, all alternatives of a Markush Group must have a common structure, which is a significant structural element. Although the luciferase variants of Groups I-IX and the luciferase variants encoded by the vectors contained in the cells of the plant of Groups X-XVIII share a common property or activity, the polypeptides are not regarded as being of similar nature because all alternatives do not share a common structure.

Also, it is noted that, according to PCT Rule 13.2 and to the guidelines in Section (f)(i)(B)(1) of Annex B of the PCT Administrative Instructions, all alternatives of a Markush Group must have a common structure, which is a significant structural element. Although the luciferase variants of Groups I-IX and the luciferase variants encoded by the vectors contained in the cells of the plant of Groups X-XVIII share a common property or activity, the proteins are not regarded as being of similar nature because the shared common structure is not a significant structural element. Applicants argue that, in view of the conservation of amino acid sequence among luciferases as shown by Ye et al., all claimed luciferase variants share a significant structural element. However, it is noted that the amino acid sequences of the claimed luciferases are not limited to those alleged to be "highly conserved" as shown in the reference of Ye et al. and instead encompass variants that do not share a significant structural element. It should also be noted that the reference of Ye et al. actually supports the position that

there is no common structure that is a significant structural element among the claimed luciferases as a review of Ye et al., particularly Figure 2, shows that there is actually very little commonly shared structure among all luciferases, thus the claimed luciferases do not share a significant structural element. Moreover, applicants have failed to identify that portion of the sequences of the luciferases of Figure 2 of the reference of Ye et al. which is considered to be a common structural that is a significant structural element that is shared among all claimed luciferases. While the recited structural characteristic, *i.e.,* at least 60 % similarity, may be common to the genus, they are clearly not a common structural feature that is a significant structural element as there is no limit to the residues that are similar to another wild-type luciferase and, moreover, there is no limit to the reference "wild-type luciferase." As such, the reference sequence can be any wild-type luciferase. Also, it is noted that, according to PCT Rule 13.2 unity of invention exists only when the shared same or corresponding special technical feature is a contribution over the prior art. The inventions do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. In this case, the claimed protein of Group I(a) was known at the time of the invention as described in greater detail below. Thus, the technical feature of Group I(a) does not make it a contribution over the prior art.

[4] The requirement is still deemed proper and is therefore made FINAL.

[5] Claims 6, 9-20, and 26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. It is noted that, while claims 9-20 were included in Group I,

these claims do not read on the elected invention and thus, have been withdrawn from further consideration.

[6] Claims 1-5, 7-8, 21-25 and 28-30 are being examined only to the extent the claims read on the elected subject matter.

Information Disclosure Statement

[7] All references cited in the information disclosure statements (IDSs), filed February 27, 2001, May 03, 2001, and October 16, 2003, have been considered by the examiner and a copy of each IDS is attached to the instant Office action.

Priority

[8] Applicant's claim for foreign priority under 35 USC § 119(a)-(d) to UK 9823468.5, filed October 28, 1998, is acknowledged. A certified copy of the foreign priority document has been filed in the instant application.

Drawings

[9] The drawings are objected to because Figure 1 is not numbered in accordance with 37 CFR 1.84(u)(1), which states, "[p]artial views intended to form one complete view, on one or several sheets, must be identified by the same number followed by a capital letter." A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Sequence Compliance

[10] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly pp. 17, 19, 21, and Figure 5 of the instant specification.

Specification/Informalities

[11] The use of the trademarks "Biotaq™" and "Advantage™ has been noted in this application (pp. 16-20). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

[12] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: --Thermostable *Photinus pyralis* Luciferase Mutant--.

[13] Applicants should identify the descriptions of the drawings at p. 15, bottom, by inserting an appropriate heading, *e.g.*, "Brief Description of the Drawings," prior to the drawing descriptions.

Claim Objections

[14] Claims 1, 4-5, and 7-8 are objected to as reciting non-elected subject matter. It is suggested that applicants amend the claims so that they no longer recite non-elected subject matter.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[15] Claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1 (claims 21-25 and 28-30 dependent therefrom), 2-5, and 7-8 are indefinite in the recitation of "60% similarity to luciferase from *Photinus pyralis,*" "the amino acid corresponding to residue 214 in *Photinus pyralis,*" "the sequence of a wild-type luciferase," "the sequence of luciferase of *Photinus pyralis,*" and "residue 214 in *Photinus pyralis* luciferase." As the specification fails to specifically define the amino acid sequence that is considered to be "a wild-type luciferase" or the sequence of a "*Photinus pyralis* luciferase", it is unclear from the claims and the specification as to the reference sequence that one is to use to determine if a particular sequence shares at least 60% similarity and to identify the amino acid residue corresponding to residue 214 of a wild-type of a variant *Photinus pyralis* luciferase. Thus, it is unclear as to the scope of claimed proteins. It is suggested that applicants clarify the meaning of the terms, by, for example, identifying the sequence by a sequence identifier.

It should be noted that the examiner can find no disclosure of the amino acid sequence of *Photinus pyralis* luciferase in the specification. In the interest of advancing prosecution, the examiner has used the sequence of *Photinus pyralis* luciferase as reported by Ye et al. (Biochem Biophys Acta 1339:39-52; cited by applicants in the specification) for purposes of search and examination.

[b] Claim 1 (claims 2-5, 7-8, 21-25, and 28-30 dependent therefrom) recites the limitation "the enzyme" in line 6 and "the luciferase enzyme" in lines 2-3. There is insufficient antecedent basis for these limitations in the claim.

[c] Claims 1 (claims 2-5, 8, 21-25, and 28-30 dependent therefrom) and 7 are indefinite in the term "similarity" as is it is unclear as to the meaning of the term. In the

interest of advancing prosecution, the term has been interpreted as meaning the level of identity shared between two amino acid sequences. Applicants are requested to clarify the meaning of the term "similarity."

[d] Claims 2 and 3 are confusing in that it is unclear as to how a polypeptide can simultaneously have the "sequence of a wild-type luciferase" and have "more than one amino acid residue is different to that of the wild-type enzyme" or "up to 50 amino acids are different to that of the wild type enzyme." It is suggested that applicants clarify the meaning of the claim.

[e] Claim 28 provides for the use of a protein, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

[16] Claims 1-5, 7-8, and 21 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim drawn to a luciferase protein and encoding nucleic acid. The claims read on a product of nature and should be amended to indicate the hand of the inventor, *e.g.*, by insertion of "purified" or "isolated". See MPEP § 2105.

[17] Claim 28 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under

35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[18] Claims 1-5, 7-8, 21-25, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

Claim 1 (claims 2-5, 7-8, and 28-30 dependent therefrom) is drawn to a genus of luciferase proteins having at least 60% similarity to *Photinus pyralis* luciferase with the amino acid at position 214 of *Photinus pyralis* luciferase replaced with another amino acid and wherein the genus of luciferase proteins has increased thermostability. Claim 21 (claims 22-25 dependent therefrom) is drawn to a genus of nucleic acids encoding said luciferase proteins.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings,

or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed recombinant polypeptides and corresponding nucleic acids, *i.e., Photinus pyralis* luciferase having a substitution of threonine at position 214 and optionally mutations at positions 215, 232, and/or 354 and a nucleic acid encoding therefor. The specification fails to describe any additional representative species of the claimed (and elected) genus of recombinant proteins. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of recombinant proteins encompasses species that are widely variant in their structures. As such, the disclosure of the single representative species of *Photinus pyralis* luciferase having a substitution of threonine at position 214 and optionally mutations at positions 215, 232, and/or 354 and a nucleic acid encoding therefor is

insufficient to be representative of the attributes and features of *all* species encompassed by the claimed genus of recombinant proteins. Given the lack of description of a representative number of recombinant proteins, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[19] Claims 1-5, 7-8, 21-25, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Photinus pyralis* luciferase having a substitution of threonine at position 214 and optionally mutations at positions 215, 232, and/or 354 and a nucleic acid encoding therefor, does not reasonably provide enablement for the broad scope of claimed luciferase proteins and encoding nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to

make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass a vast number of luciferase polypeptides having increased thermostability and nucleic acids encoding therefor. The scope of claimed polypeptides/nucleic acids encompasses mutants and variants having a substantial number of alterations including additions, deletions, substitutions, and insertions. The broad scope of claimed polypeptides and polynucleotides is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides and polynucleotides broadly encompassed by the claims. In this case the disclosure is limited to a *Photinus pyralis* luciferase having a substitution of threonine at position 214 and optionally mutations at positions 215, 232, and/or 354 and a nucleic acid encoding therefor.

- The nature of the invention: The nature of the invention involves the alteration of a known amino acid sequence, *i.e.*, the amino acid sequence of *Photinus pyralis* luciferase, (apparently) as reported by Ye et al. (*supra*), to arrive at a mutant luciferase amino acid sequence that has an improvement in its thermostability as compared to the unaltered amino acid sequence.

- The lack of working examples and direction in the specification: The specification provides only a single working example of the elected luciferase polypeptide, i.e., a *Photinus pyralis* luciferase having substitution of threonine at position 214 and the

specification teaches the additional working examples of *Photinus pyralis* luciferase having substitution of threonine at position 214 and 215, 232, and/or 354. However, these working examples fail to provide the necessary guidance for making the entire scope of claimed luciferase polypeptides and polynucleotides. The specification fails to provide guidance regarding those nucleotides/amino acids of luciferase that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining luciferase activity with an additional expectation of having increased thermostability as compared to a corresponding wild-type luciferase.

- The state of the art supports a high level of unpredictability: The nucleotide sequence of an encoding nucleic acid determines the corresponding encoded protein's structural and functional properties. Predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail

above. The level of unpredictability is further compounded as one must not only have an expectation of obtaining a polypeptide/encoding polynucleotide with luciferase activity, but also having that ability to emit light at a different wavelength and/or having enhanced thermostability as compared to a corresponding wild-type luciferase. The state of the art provides evidence for the high degree of unpredictability in altering a polynucleotide sequence with an expectation that the encoded polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The teachings of Branden et al. are manifest in the reference of Witkowski et al. (*Biochemistry* 38:11643-11650), who teach that a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647). Thus, the prior art acknowledges the unpredictability of altering a protein-encoding sequence with an expectation of obtaining a protein having a desired function.

- The amount of experimentation required is undue: While methods of generating variants of a given polypeptide by altering the encoding nucleic acid sequence are known, *e.g.*, by site-directed mutagenesis, it is not routine in the art to screen for all

polypeptides and polynucleotides having a *substantial* number of substitutions or modifications as encompassed by the instant claims.

Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high degree of unpredictability as evidenced by the prior art, and the significant amount of experimentation required, undue experimentation would clearly be necessary for a skilled artisan to make and/or use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the

> invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

[20] Claims 1-2, 4-5, 7, and 21-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Database EMBL Accession Number D25415. Claims 1-2, 4-5, and 7 are drawn to a luciferase protein having at least 60% similarity to *Photinus pyralis* luciferase with the amino acid at position 214 of *Photinus pyralis* luciferase replaced with another amino acid and wherein the luciferase protein has increased thermostability. Claims 21-24 are drawn to a nucleic acid encoding said luciferase protein, a vector comprising said nucleic acid, and a host cell comprising said vector.

Database EMBL Accession Number D25415 teaches a nucleic acid sequence encoding a P. pennsylvanica luciferase polypeptide and the amino acid sequence of the encoded polypeptide. The encoded polypeptide has an asparagine at the position corresponding to position 214 of *Photinus pyralis* luciferase (see Appendix A; note the amino acid sequence shown in Appendix A is the encoded polypeptide of Database EMBL Accession Number D25415, which has Database EMBL Accession Number Q94696). This anticipates claims 1-2, 4-5, 7, and 21-24 as written.

It is acknowledged that the reference of Database EMBL Accession Number D25415 fails to teach the vector comprising their nucleic acid, *i.e.*, pPFL19, has been used to transform a host cell. However, transformation of a host cell, particularly an *E. coli* host cell, with a vector comprising a ligated nucleic acid fragment, is an inherent step in the cloning process.

It is further acknowledged that the reference of Database EMBL Accession Number D25415 fails to teach that the disclosed protein has an increased thermostability relative to wild-type *Photinus pyralis* luciferase. However, since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (*i.e.*, that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

[21] Claims 1-2, 4-5, 7, 21-24, and 28-30 are rejected under 35 U.S.C. 102(e) as being anticipated by Wood et al. (US Patent Application Publication 2003/0068801; "Wood"). Claims 1-2, 4-5, 7, and 21-24 are drawn to the invention as stated above. Claims 28-30 are drawn to the use of the protein of claim 1 in a bioluminescence assay and a kit comprising the claimed protein.

Wood teaches thermostable P. pennsylvanica luciferase polypeptides of SEQ ID NO:27-28, 30, and 32-33 (for a representative alignment with SEQ ID NO:32, see Appendix B) and corresponding encoding nucleic acid, a vector comprising said nucleic acid, a host cell, including a prokaryotic host cell, comprising said vector (see, *e.g.*, paragraph [0009]), a method of using their protein in a luminescence assay for detecting ATP and luciferin in a sample using their luciferase (see, *e.g.*, paragraph [0073]), and teach an embodiment of their invention as being a kit comprising their protein (see, *e.g.*, paragraph [0009]). This anticipates claims 1-2, 4-5, 7, 21-24, and 28-30 as written.

It is acknowledged that the reference of Wood fails to teach that their disclosed proteins have an increased thermostability relative to wild-type *Photinus pyralis* luciferase. However, since the Office does not have the facilities for examining and comparing applicants' protein with the proteins of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (*i.e.*, that the proteins of the prior art do not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[22] Claim(s) 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gustafson et al. (US Patent 5,196,524; "Gustafson") in view of Wood. Claim 25 is drawn to a plant cell transformed with a vector comprising a nucleic acid encoding a luciferase protein having at least 60% similarity to *Photinus pyralis* luciferase with the amino acid at position 214 of *Photinus pyralis* luciferase replaced with another amino acid and wherein the luciferase protein has increased thermostability.

Gustafson teaches transformation of a plant cell with a vector comprising a nucleic acid encoding luciferase (columns 27-29).

Wood discloses the teachings as described above.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Gustafson and Wood to replace the luciferase-encoding nucleic acid in the vector of Gustafson with the nucleic acid encoding a luciferase as taught by Wood. One would have been motivated for to replace the luciferase-encoding nucleic acid in the vector of Gustafson with the nucleic acid encoding a luciferase as taught by Wood in order that the plant cells express a relatively more thermostable luciferase. One would have a reasonable expectation of success for to replacing the luciferase-encoding nucleic acid in the vector of Gustafson with the nucleic acid encoding a thermostable luciferase as taught by Wood because of the results of Wood and Gustafson. Therefore, claim 25, drawn to the plant cell as described above would have been obvious to one of ordinary skill in the art.

Double Patenting Rejection(s)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[23] Claims 1-5, 7-8, and 21-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-10, 14, 17-19 and 6-23 of copending Application No. 10/111,723 (the '723 Application). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-5, 7-8, and 21-23 of the instant application and claims 1-4, 6-10, 14, 17-19 and 6-23 of the '723 Application are both directed to mutant *Photinus pyralis* luciferase proteins having enhanced thermostability, encoding nucleic acids, vectors, and host cells. The claims differ in that claims 1-5, 7-8, and 21-23 of the instant application are limited to a *Photinus pyralis* luciferase with at least a mutation at position 214, whereas the *Photinus pyralis* luciferase of claims 1-4, 6-10, 14, 17-19 and 6-23 of the '723 Application is limited to having at least a mutation at position 357. The specification of the '723 Application supports an embodiment that would anticipate claims 1-5, 7-8, and 21-23 herein, *i.e.*, a *Photinus pyralis* luciferase having mutation at position 214 (see, *e.g.*, Example 12 at pp. 42-43 of the '723 Application specification).

Claims 1-5, 7-8, and 21-23 cannot be considered to be patentably distinct over claims 1-4, 6-10, 14, 17-19 and 6-23 of the '723 Application when there is a specifically recited embodiment in the '723 Application that would anticipate claims 1-5, 7-8, and 21-23 of the instant application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Citation of Relevant Art

[24] The following reference is cited as being relevant to the instant application. This reference was published after the effective filing date of the instant application and as such, is not available as prior art.

Tisi et al. Bioluminescence and Chemiluminescence: Proceedings of the Symposium on Bioluminescence and Chemiluminescence, 12th, Cambridge, UK, April 5-9, 2002, 57-60 (abstract only; 2003:108770 CAPLUS).

Conclusion

[25] Status of the claims:

- Claims 1-26 and 28-30 are pending.
- Claims 6, 9-20, and 26 are withdrawn from consideration.
- Claims 1-5, 7-8, 21-25, and 28-30 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's

supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 872-9306. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

12-9-04

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1652

APPENDIX A

```
ID   Q94696      PRELIMINARY;      PRT;   552 AA.
AC   Q94696;
DT   01-FEB-1997 (TrEMBLrel. 02, Created)
DT   01-FEB-1997 (TrEMBLrel. 02, Last sequence update)
DT   01-OCT-2003 (TrEMBLrel. 25, Last annotation update)
DE   Luciferase.
GN   LUC.
OS   Photuris pennsylvanica (Pennsylvania firefly).
OC   Eukaryota; Metazoa; Arthropoda; Hexapoda; Insecta; Pterygota;
OC   Neoptera; Endopterygota; Coleoptera; Polyphaga; Elateriformia;
OC   Cantharoidea; Lampyridae; Photuris.
OX   NCBI_TaxID=41716;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Lantern;
RA   Zenno S., Shiraishi S., Inouye S., Saigo K.;
RT   "Cloning, nucleotide sequence and expression of two cDNAs encoding for
RT   luciferase from Photuris firefly.";
RL   Submitted (NOV-1993) to the EMBL/GenBank/DDBJ databases.
DR   EMBL; D25415; BAA05005.1; -.
DR   HSSP; P08659; 1LCI.
DR   GO; GO:0003824 ; F:catalytic activity; IEA.
DR   GO; GO:0008152; P:metabolism; IEA.
DR   InterPro; IPR000873; AMP-bind.
DR   Pfam; PF00501; AMP-binding; 1.
DR   PROSITE; PS00455; AMP_BINDING; 1.
SQ   SEQUENCE   552 AA;  61000 MW;  85C14ED52BD5366A CRC64;
```

```
  Query Match             71.1%;  Score 2025;  DB 5;  Length 552;
  Best Local Similarity   69.6%;  Pred. No. 6e-145;
  Matches  382;  Conservative   69;  Mismatches   96;  Indels    2;  Gaps    2;

Qy          3 MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTDAHIEVNITYAEYFEMS 62
              |    ||  || |:||||:||||||||:|: ||| ||||:|:|| | |: :|| |: :::
Db          1 MSIENNILIGPPPYYPLEEGTAGEQLHRAITRYAAVPGTLAYTDVHTELEVTYKEFLDVT 60

Qy         63 VRLAEAMKRYGLNTNHRIVVCSENSLQFFMPVLGALFIGVAVAPANDIYNERELLNSMNI 122
              ||||||| |||  | | ||||| :|||||  ||:|||| || ||||||||| ||::|
Db         61 CRLAEAMKNYGLGLQHTISVCSENCVQFFMPVCAALYIGVATAPTNDIYNERELYNSLSI 120

Qy        123 SQPTVVFVSKKGLQKILNVQKKLPIIQKIIIMDSKTDYQGFQSMYTFVTSHLPPGFNEYD 182
              ||||||| |:  ||||| || :||:|:|||::|:| || |:||| :|:  |:|  ||
Db        121 SQPTVVFTSRNSLQKILGVQSRLPVIKKIIMLDTKKDYLGYQSMQSFMKEHVPANFNVSA 180

Qy        183 FVPESFDRDKTIALIMNSSGSTGLPKGVALPHRCACVRFSHARDPIFGNQIIPDTAILSV 242
              | | ||| |: :| ||||||||||||||| : ||    |||| |||:||||||||| ||
Db        181 FKPLSFDLDR-VACIMNSSGSTGLPKGVPISHRNTTYRFSHCRDPVFGNQIIPDTTILCA 239

Qy        243 VPFHHGFGMFTTLGYLICGFRVVLMYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKSTL 302
              ||||| || || |||:|||| ||||||| | |||::||||| ||||:|||: :| ||: |
Db        240 VPFHHAFGTFTNLGYIICGFHVVLMYRFNEHLFLQTLQDYKCQSALIVPTVLAFLAKNPL 299

Qy        303 IDKYDLSNLHEIASGGAPLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILITPKGDFKPG 362
              :||||||:|||||||||||||: |  |||| |||||||||||||| ||:|| :|:||||
Db        300 VDKYDLSHLHEIASGGAPLSKEISEIAAKRFKLPGIRQGYGLTETTCAIVITAEGEFKPG 359

Qy        363 AVGKVVPFFEAKVVDLDTGKTLGVNQRGELCVRGPMIMSGYVNNPEATNALIDKDGWLHS 422
              ||||||||:  ||:||:||| || |:|||:|  ||||| ||:|||||  :||::||:||
Db        360 AVGKVVPFYSLKVLDLNTGKKLGPNERGEICFTGPMIMKGYINNPEATREIIDEEGWIHS 419

Qy        423 GDIAYWDEDEHFFIVDRLKSLIKYKGYQVAPAELESILLQHPNIFDAGVAGLPDDDAGEL 482
              ||| |:||| | :|||||||||||||||| |||||::||||| | ||||||:||: ||:|
Db        420 GDIGYFDEDGHVYIVDRLKSLIKYKGYQVPPAELEALLLQHPFIEDAGVAGVPDEVAGDL 479

Qy        483 PAAVVVLEHGKTMTEKEIVDYVASQVTTAKKLRGGVVFVDEVPKGLTGKLDARKIREILI 542
              | |||||: ||::|||||  |||| |||::||||||| || |||||  |||:| |||:||||
```

```
Db        480 PGAVVVLKEGKSITEKEIQDYVAGQVTSSKKLRGGVEFVKEVPKGFTGKIDTRKIKEILI 539

Qy        543 KAKKGGKSK 551
              ||:| ||||
Db        540 KAQK-GKSK 547
```

APPENDIX B

```
RESULT 7
US-09-838-469-32
; Sequence 32, Application US/09838469
; Publication No. US20030068801A1
; GENERAL INFORMATION:
;  APPLICANT: Wood, Keith V.
;  APPLICANT:  Hall, Mary P.
;  APPLICANT:  Promega Corporation
;  TITLE OF INVENTION: THERMOSTABLE LUCIFERASES AND METHODS OF PRODUCTION
;  FILE REFERENCE: 341.006US1
;  CURRENT APPLICATION NUMBER: US/09/838,469
;  CURRENT FILING DATE:  2001-04-19
;  PRIOR APPLICATION NUMBER: US/09/156,946
;  PRIOR FILING DATE: 1998-09-18
;  NUMBER OF SEQ ID NOS: 41
;  SOFTWARE: PatentIn Ver. 2.0
; SEQ ID NO 32
;   LENGTH: 547
;   TYPE: PRT
;   ORGANISM: Beetle
US-09-838-469-32

  Query Match             84.7%;  Score 2412.5;  DB 10;  Length 547;
  Best Local Similarity   83.6%;  Pred. No. 5.3e-235;
  Matches  460;  Conservative   37;  Mismatches   50;  Indels    3;  Gaps    1;

Qy          3 MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTDAHIEVNITYAEYFEMS 62
              |||||||  ||||||||||||||||||||||||| |||||||||||| |||||||:|||||:
Db          1 MEDAKNIMHGPAPFYPLEDGTAGEQLHKAMKRYAQVPGTIAFTDAHAEVNITYSEYFEMA 60

Qy         63 VRLAEAMKRYGLNTNHRIVVCSENSLQFFMPVLGALFIGVAVAPANDIYNERELLNSMNI 122
               ||||  ||||||    | | |||||||||||||| |||||||  ||  |||||||||  ||::|
Db         61 CRLAETMKRYGLGLQHHIAVCSENSLQFFMPVCGALFIGVGVASTNDIYNERELYNSLSI 120

Qy        123 SQPTVVFVSKKGLQKILNVQKKLPIIQKIIIMDSKTDYQGFQSMYTFVTSHLPPGFNEYD 182
              ||||:|  ||: ||||| ||||||||||:|:||: || | ||||:|: |||| ||||||
Db        121 SQPTIVSCSKRALQKILGVQKKLPIIQKIVILDSREDYMGKQSMYSFIESHLPAGFNEYD 180

Qy        183 FVPESFDRDKTIALIMNSSGSTGLPKGVALPHRCACVRFSHARDPIFGNQIIPDTAILSV 242
              ::|:||||:   |||||||||||||||| | |:  |||||| |||:||||||||||||:|
Db        181 YIPDSFDRETATALIMNSSGSTGLPKGVELTHQNVCVRFSHCRDPVFGNQIIPDTAILTV 240

Qy        243 VPFHHGFGMFTTLGYLICGFRVVLMYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKSTL 302
              :|||||||||||||| ||||:|||||||||||||||||||||||||||||||||||||||
Db        241 IPFHHGFGMFTTLGYLTCGFRIVLMYRFEEELFLRSLQDYKIQSALLVPTLFSFFAKSTL 300

Qy        303 IDKYDLSNLHEIASGGAPLSKEVGEAVAKRFHLPGIRQGYGLTETTSAILITPKGDFKPG 362
              :|||||||||||||||||:|||||||||| ||||||||||||||||:|||:|| |||
Db        301 VDKYDLSNLHEIASGGAPLAKEVGEAVAKRFKLPGIRQGYGLTETTSAIIITPEGDDKPG 360

Qy        363 AVGKVVPFFEAKVVDLDTGKTLGVNQRGELCVRGPMIMSGYVNNPEATNALIDKDGWLHS 422
              | ||||||| ||:|||||||||||||||||:||||| |||||||||:|||||||||||
Db        361 ACGKVVPFFSAKIVDLDTGKTLGVNQRGELCVKGPMIMKGYVNNPEATSALIDKDGWLHS 420

Qy        423 GDIAYWDEDEHFFIVDRLKSLIKYKGYQVAPAELESILLQHPNIFDAGVAGLPDDDAGEL 482
              |||||:|:| ||||||||||||||||| |||||||||| ||||||||:|| |||||
Db        421 GDIAYYDKDGHFFIVDRLKSLIKYKGYQVPPAELESILLQHPFIFDAGVAGIPDPDAGEL 480

Qy        483 PAAVVVLEHGKTMTEKEIVDYVASQVTTAKKLRGGVVFVDEVPKGLTGKLDARKIREILI 542
              |||||||| ||||||:|::|||| ||| :|:||||| |||||||||||:| |||||||:
Db        481 PAAVVVLEEGKTMTEQEVMDYVAGQVTASKRLRGGVKFVDEVPKGLTGKIDGRKIREILM 540

Qy        543 KAKKGGKSKL 552
                |   ||||
Db        541 MGK---KSKL 547
```